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Monitoring of metals and metalloids from maternal and cord blood samples in a population from Seville (Spain)

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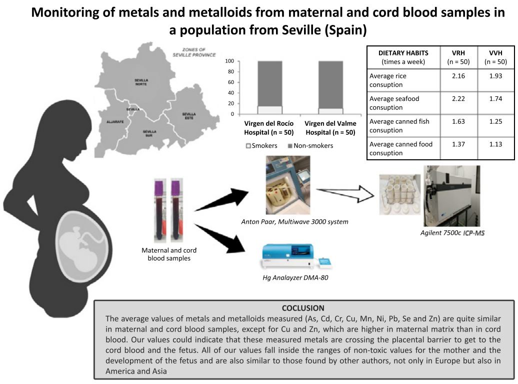
HIGHLIGHTS

- Monitoring of metals and metalloid by ICP-MS was made in maternal and cord blood samples.
- A positive correlation between maternal and cord blood was found between metals.
- The strongest correlation was found for Hg.
- No correlations were observed between Cd, Cr, Pb and Ni levels and smoking habit.
- Detected levels of Pb are acceptable for maternal and cord blood.

GRAPHICAL ABSTRACT



Monitoring of metals and metalloids from maternal and cord blood samples in a population from Seville (Spain)

DIETARY HABITS (times a week)	VRH (n = 50)	VVH (n = 50)
Average rice consuption	2.16	1.93
Average seafood consuption	2.22	1.74
Average canned fish consuption	1.63	1.25
Average canned food consuption	1.37	1.13

COCLUSION

The average values of metals and metalloids measured (As, Cd, Cr, Cu, Mn, Ni, Pb, Se and Zn) are quite similar in maternal and cord blood samples, except for Cu and Zn, which are higher in maternal matrix than in cord blood. Our values could indicate that these measured metals are crossing the placental barrier to get to the cord blood and the fetus. All of our values fall inside the ranges of non-toxic values for the mother and the development of the fetus and are also similar to those found by other authors, not only in Europe but also in America and Asia

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ABSTRACT

Nowadays there is an increasing concern about exposition during prenatal stage to environmental pollutants such as metals, that make pregnant women a vulnerable group of population. Numerous studies have shown associations between the prenatal exposition to some metals and an impact on cognitive, motor and intellectual development of the child. Metals and metalloid are ubiquitous in the environment and pregnant women are exposed to them though their diet, lifestyle factors or occupational and environmental sources. One hundred of maternal and one hundred of cord blood samples were obtained at delivery from pregnant women after signing of the informed consent to determine simultaneously levels of Al, As, Cd, Cr, Cu, Hg, Mn, Ni, Pb, Se and Zn by ICP-MS. Among these metals, essential ones (Cu, Mn, Se and Zn) can have health beneficial effects at low levels, however, in high concentration are potentially toxic. On the other hand, elements such as Al, As, Cd, Hg, Pb are classified as toxic metals, no matter what its concentration was.

The aim of this study was to find the potential relationships between these metals and metalloid levels, newborn's parameters, pregnancy details and the epidemiologic information obtained using a questionnaire data from the participant pregnant women from Seville (Spain).

A $n = 100$ of participants have been enrolled, 15.6 % of the women from Virgen del Rocio Hospital were smokers during pregnancy but only 11.1 % from Virgen de Valme had the habit. Dietary habits of all participants from both

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hospital were quite similar in average rice, fish and canned food consumption. The characteristics of newborns were also quite similar for both hospitals. A positive correlation between maternal and cord blood was found between all metals except for Cr and Cu. The strongest correlation was found for Hg ($r = 0.779$, $p < 0.005$). Positive but weaker correlations between maternal blood and lifestyle habits were also established.

1. Introduction

Humans are constantly exposed to metals and metalloids, that are present in the environment and can be released from either natural or anthropogenic sources such as industrial activity, accumulating in the environment for many years (Lozano et al., 2022). Exposure to these metals/metalloids can come from different sources, from drinking water to diet including fish, sea food, meat, rice or vegetables (Weyde et al., 2021), or lifestyle habits like smoking, alcohol consumption or drug abuse and also via inhalation of contaminated air (Cerrillos et al., 2019; Stojsavljević et al., 2021; Weyde et al., 2021). This exposure is known to be one of the most harmful risk factors for the human health and has a special importance in vulnerable stages such as pregnancy or lactation (Stojsavljević et al., 2021). One of the most sensitive phases of development is the early prenatal life, when the embryo is susceptible to all kinds of external influences, even when the exposure is minimal (Cerrillos et al., 2019). Most studies are related with the effect of metals on neurocognitive development focused on the impact of this exposure in children's intelligence (Lee et al., 2021). These substances are able to reach the fetus trough the placenta, even from the earliest times of gestation (Karakis et al., 2021; Lozano et al., 2022) being this the principal reason why maternal blood levels of metals/metalloids can be used as an approximation of metal and metalloid levels on the children and its possible health outcomes (Karakis et al., 2021). Toxic metals/metalloids exposition in utero through trans-placental transport and essential elements in an inadequate or excessive levels can cause a negative impact on the offspring health since birth defects to cancer, allergy or neurodevelopmental disorders and cognitive impairments (Weyde et al., 2021). Essential trace elements such as calcium (Ca), cobalt (Co), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), selenium (Se), sodium (Na), and zinc (Zn) play an important role in the biological processes of human body. These biological processes, like the protective part against oxidative damage to cellular respiration or cell signaling and apoptosis (Karakis et al., 2021; Lee et al., 2021) can play very important roles in fetal growth and development of the fetus. For instance, Zn is a component of many proteins and interacts in several biological processes; Fe is also the main component of hemoglobin and can increase birth weight, being closely related to Cu that contributes with the absorption and metabolism of Fe. Both of them also play an important role in the reactive oxygen species (ROS) generation though Fenton reaction (Gautam et al., 2021). Cu is closely related to intrauterine inflammation and the induction of oxidative stress resulting in an important role in fetal growth (Wu et al., 2021). Mg acts as enzyme cofactor and activator and its deficiency can cause a range of morbidity as it may interfere with fetal growth and development but can also negatively affect the developing fetus at higher levels (Lee et al., 2021). Mn is a necessary constituent of many proteins that play essential roles in metabolism such as mitochondrial enzymes or the very known superoxide dismutase (SOD) and other like pyruvate carboxylase and glutamine synthetase (GS). Although it play many important roles, Mn is known for its neurotoxicity, being an excessive exposure related to central nervous system disorders characterized by psychological and neurological activities (Bjørklund et al., 2017). A high exposure to Mn during pregnancy may also cause toxic effect on the developing fetus, specially related to neurodevelopmental problems and poor neurobehavioral performance (Bjørklund et al., 2017; Lee et al., 2021). All these essentials elements do not only play important independent roles but also act as part of the metabolism and in creating important hormones such thyroid hormones (THs) that can be related to the risk of developing hypothyroidism, hyperthyroidism and thyroid cancer (Wu et al., 2021). Non-essential metals/metalloids are dangerous for human health, and their adverse effects in the developing fetus are related to the affinity for the same transporters that essential metals/metalloids use (Lozano et al., 2022). The exposure to these metals/metalloids in children is more significant because their detoxification mechanism are yet to be completely developed (Tatsuta et al., 2020). Metals and metalloids such as lead (Pb), arsenic (As), and mercury (Hg) head the list for most toxic metals for humans, closely followed by aluminum (Al), cadmium (Cd), chromium (Cr), nickel (Ni) and others being highly toxic for humans and can cause severe morbidities (Karakis et al., 2021). Many studies have stated that heavy metals, like Pb, Cd and Hg can play the role of neurotoxins and have a negative impact in neurodevelopment (Lee et al., 2021), but they do not only have neurological effect but Pb also can lead to the development of several adverse effects on the hematologic, gastrointestinal, cardiovascular and renal system (CDC, 2010; Tatsuta et al., 2020). Maternal blood Pb levels can also play an important role during delivery, since values around 100 μg/L are studied to increase risks of hypertension, that can lead to preeclampsia, and spontaneous abortion, also reducing neurobehavioral development in offspring (Li et al., 2019). Cd levels in maternal blood have also been reported to be inversely related to birth weight and directly related to the risk of neural tube defects in the newborn (Li et al., 2019). As, Cd, Hg or Ni also have been reported to be related to congenital defects at birth and specifically Cd and As have been adversely linked to small-for-gestational age (SGA) status (Karakis et al., 2021).

The aim of this study was to find the potential relationships between these metals and metalloid levels, newborn's parameters, pregnancy details and the epidemiologic information obtained using a questionnaire data from the participant pregnant women from Seville (Spain).

2. Material and methods

2.1. Study population

The present study is based on ongoing prospective birth cohorts in the south of Spain. The cohorts were established in the catchment area two of the main Hospitals in Seville, Hospital Universitario Virgen del Rocío and Hospital Universitario Virgen de Valme. The expectant parents planning to give birth in these two hospitals since July 2020 to October 2021 were informed at their ultrasound visit (gestational week 40) and were asked for signing the informed consent. One hundred healthy women older than 18 and younger than 40 years were recruited to participate in this study. To be included, parents had to be residents in the hospital reference area for at least the last 5 years, and be able to communicate in Spanish. Also women must not have followed any assisted reproduction program and have a single pregnancy, regardless of whether they are nulliparous or multiparous. Women who suffered from chronic hypertension, any type of diabetes, thyroid disorders or chronic renal or cardiac disease during pregnancy were excluded. The study was approved by Coordinating Committee for the Ethics of Biomedical Research of Andalusia in June 2020 (1479-N-20) and written informed consent was obtained from the participants.

Once signed the informed consents, enrolled women, were asked to complete a detailed questionnaire about demographic (age, hospital of reference, place of birth…), lifestyles, dietary habits, and previous medical history.

This questionnaire includes 43 questions, divided in different sections. We have classification data such as the identification number but also date of birth and reference hospital, that allows us to classify the patient but also personal data like place of birth, race, place of residence, postal code… There is also questions about personal habits like smoking habits or use of pesticides at home. For dietary habits questions included range from type of diet to pieces of fruit and vegetables consumed per day. Some of this questions are closed, with stablished yes or no answers and some of them are even mandatory to answer in order to move along the questionnaire, such as smoking habits. Some of the questions are completely open like job description.

2.2. Collection and storage of biological samples

All enrolled women had an uncomplicated vaginal delivery. None of the women suffered from complications during their pregnancies. No perinatal death, birth defects or maternal serious health problems were seen at delivery or postpartum.

Maternal and cord blood (8 mL each) was collected just after the delivery in the Department of Gynaecology and Obstetrics in both Hospitals (Seville, Spain). Collected biomaterial was refrigerated at 4 °C during transportation and immediately stored at −80 °C before analysis. Great care was taken to avoid contamination during all analytical stages (biological media sampling, transportation, storage, sample preparation and analysis).

2.3. Standards and chemical

All solutions were prepared using deionized water (18 MΩ-cm at 25 °C) obtained from a Milli-Q system (Millipore, Bedford, MA, USA). All the laboratory ware (transfer pipettes, centrifuge tubes, plastic bottles, vials and glassware material) was cleaned by soaking in 20 % v/v HNO_3 reagent grade for at least 4 h and rinsing three times with deionized water, according to the USEPA method 200.8 and drying in a laminar flow hood. Suprapur® quality HNO_3 (65 %), HCl (30 %), and H_2O_2 (30 %) were purchased form Merck (Merck- Millipore, Merck KGaA, Darmstadt, Germany) and used as received.

The reagent blank solution consisted of 1 % HNO_3, 0.2 % HCl and gold. The reagent blank is prepared by diluting 65 % Suprapur® nitric acid and 30 % Suprapur® hydrochloric acid with the appropriate volume of deionized water.

Vanadium (V), rhodium (Rh) and bismuth (Bi) were used as internal standards to correct for instrumental drift. All internal standards were added online in the form of a 1 μg/mL multielement solution in 1 % HNO_3. V corrects for Mn, Rh is suitable for Cd and Bi was added to correct for Pb.

2.4. Metals and metalloids measurement

The concentrations of 9 metals/metalloids (As, Cd, Cr, Cu, Mn, Ni, Pb, Se and Zn) were assessed in maternal and cord blood samples collected during delivery. An Anton Paar, Multiwave 3000 system was used to digest blood.

Detection limits were calculated through the concentration of an element, giving a signal equal three times the standard deviation of a series of ten measurements of the blank solution at the element peak. The average detection limits un blood were 10 ng/mL for Hg, 0.10 ng/mL for Cd, 0.56 ng/mL for Cr, 0.51 ng/mL for Cu, 0.21 ng/mL for Mn, 0.25 ng/mL for Ni, 0.13 ng/mL for Pb, 0.19 ng/mL for Se and 5.46 ng/mL for Zn.

All digestions were carried out in polytetrafluoroethylene (PTFE) digestion vessels. Before digestion, samples were let to defrost at 4 °C overnight, and then were thoroughly homogenized. For predigesting, 1 mL of blood was used and 2 mL of HNO_3 were added. After a two-hour period of incubation, 2 mL of H_2O_2 were added, to incubate again for 2 h. Afterwards, they were kept at 4 °C. The digestion program for 8 vessels consisted of an initial power ramp from 0 to 800 W of 10 min, followed by a continuous power stage of 800 W for 20 min, and a final cooling stage of 15 min, with no power applied. For digestion, the sample was transferred to a digestion vessel and 4 mL of water and another 1 mL of bidestilated HNO_3 were used to gather the remains. All the measured samples were prepared in triplicate.

2.5. Instrumentation

Inductively coupled plasma mass spectrometric measurements were performed with an Agilent 7500c ICP-MS (Agilent Technologies, Tokyo, Japan) equipped with an Integrated Autosampler and an Octupole Reaction System (ORS). The ORS was pressurized with helium in collision mode for the determination of Mn and Cd, and argon in standard mode for the determination of Pb. Standard Ni sampler and skimmer cones (1.0 and 0.7 mm i.d., respectively) were used. Sample introduction was performed with a Babington PEEK (poly-ether-ether-ketone) nebulizer combined with a quartz Scott-type double pass spray chamber (Agilent Technologies, Tokyo, Japan). The spray chamber was water-cooled at 2 °C to ensure temperature stability and to reduce vapors entering the torch. The ICP torch consists of a three-cylinder assembly, with injector diameter 2.5 mm. The Shield Torch was used throughout the whole analysis. All instrumental parameters were optimized daily while aspirating the tuning solution.

2.6. Determination of total Hg in whole blood

Levels of Hg were measured directly from a 200 μL blood sample by a DMA-80 direct mercury analyzer. Also, in this case, all the measured samples were prepared in triplicate.

2.7. Statistical analyses

Continuous variables were expressed in the form of mean and standard deviation or median and percentiles 25 and 75 were used when our data presented an accentuated asymmetry. Qualitative variables have been expressed in the form of frequencies and percentages. To determine if data is well-modeled by a normal distribution, the normality test run was Shapiro-Wilk. Because the variables were not distributed normally, non-parametric statistics were used throughout the study. Spearman's coefficients were used to correlate maternal and cord blood metals/metalloids levels. The Mann-Whitney *U* test was used to analyze the between-group differences for lifestyle habits and some metal levels. The data were recorded in Excel 16.55 accounting sheet, while IBM SPSS Statistics 26 was used for the statistical analysis. The level of significance for accepting or rejecting statistical hypotheses was defined as $p = 0.05$.

3. Results

3.1. Sociodemographic characteristics of the included mothers and infants

The mean age of the participants ($N = 100$) was 34.90 (± 0.79) years (range 23 to 40 years) for Virgen del Rocío Hospital (VRH) participants and 34.59 (± 1.10) years for Virgen del Valme Hospital (VVH) (range 25 to 40 years). About distribution in different residence areas, 33 % of the participants live in the capital, 46 % in different villages form Sevilla Sur area and 21 % in villages from Aljarafe area (Fig. 1).

Concerning lifestyle habits (Table 1), 15.6 % of the enrolled women from VRH declared to smoke during the whole pregnancy period with an average of 5 cigarettes per day. Similarly, 11.1 % of the participants from VVH stated smoking habit during pregnancy, with an average of 6 cigarettes per day. Regarding dietary habits, 100 % of the pregnant women stated to follow a Mediterranean diet. The following average were calculated from VRH participants: rice consumption 2.16 (± 1.48) times per week, sea-food consumption 2.22 (± 1.26) times per week, being the white ones the most consumed, canned fish consumption 1.63 (± 1.30) times a week and 1.37 (±1.74) times per week consumption of other canned foods different from fish. Regarding enrolled women from VVH, the calculated average were rice consumption a little bit lower (1.93 (± 0.68) times per week), sea-food consumption of 1.74 (± 0.59) times per week, being blue fish the most consumed, canned fish consumption 1.25 (± 0,89) and 1.13 (± 0.99) times per week consumption of other canned foods different from fish.

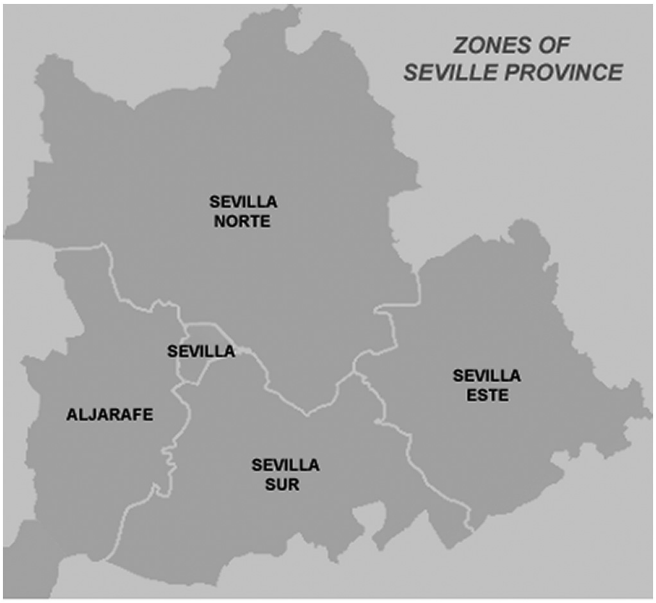

Fig. 1. Maps of Seville where the different studied areas are shown.

Characteristics from newborns was very similar in both hospitals (Table 2), thus, average cord pH values was around 7.3 for both hospitals (VRH: 7.31 (± 0.05) and VVH: 7.28 (±0.07)). For newborns weight, VVH had values a little bit lower with an average of 3458.55 (± 425.490) grams in comparison with VRH average, 3506.33 (± 444.85) grams. Similarly, newborns' height average values in both hospitals were very closed, 50.55 (± 1.70) cm VRH and 49.31 VVH (± 6.90) cm, respectively. There neither was significant differences in head circumference average values between hospitals, VRH 34.95 (± 1.44) and VVH 35.15 (± 1.49) centimeters.

3.2. Metal and metalloid levels in the studied population

Descriptive statistics of metals and metalloid levels in maternal and cord blood are presented in Tables 3 and 4. The median level of Hg found in maternal blood (3.03 μg/L) was lower than the median level found in cord blood (4.24 μg/L), being the highest value for Hg in cord blood (52.15 μg/L) a lot higher than the one found in maternal blood (28.51 μg/L). A similar scheme is followed for Ni, the only other metals measured where the values for maternal blood (18.44 μg/L) are lower than the ones found for cord blood (20.14 μg/L) but with a higher maximum found in maternal blood (251.22 μg/L). The median values of Cu and Zn found in maternal blood (1632.10 μg/L and 5088 μg/L) were almost three times fold higher than the ones found in cord blood in both cases (655.08 μg/L for Cu and 2220.70 μg/L for Zn). As, Cd, Cr, Mn, Pb and Se had quite similar but a little bit higher values for maternal blood (10.60 μg/L, 0.82 μg/L, 216.24 μg/L, 48.76 μg/L, 10.18 μg/L and 119.78 μg/L) than for cord blood (10.16 μg/L, 0.73 μg/L, 208.82 μg/L, 45.10 μg/L, 9.51 μg/L and 117.66 μg/L).

Table 1
Sociodemographic and lifestyle data from both VRH and VVH.

		Virgen del Rocío Hospital (n = 50)	Virgen del Valme Hospital (n = 50)
	Age (years)	34.9 (± 0.79)	34.59 (± 1.10)
	People in the family nucleus	2.94 (± 0.16)	3.19 (±0.18)
Educational level	Primary education	6.30 %	11.10 %
	Secondary education	15.60 %	22.20 %
	Higher education	78.10 %	66.70 %
Employment situation	Unemployed	18.80 %	14.80 %
	Employed	81.30 %	85.20 %
Smoking habits	Smokers	15.60 %	11.10 %
	Non-smokers	84.40 %	88.90 %
Dietary habits	Mediterranean	100.00 %	100.00 %
	Vegetarian	0.00 %	0.00 %
	Vegan	0.00 %	0.00 %
	Average weekly rice consumption (times a week)	2.16 (± 1.48)	1.93 (± 0.68)
	Average weekly seafood consumption (times a week)	2.22 (± 1.26)	1.74 (± 0.59)
	Most consumed type of seafood	White fish	Blue fish
	Average weekly canned fish consumption (times a week	1.63 (± 1.30)	1.25 (± 0.89)
	Average weekly canned food consumption (times a week)	1.37 (± 1.74)	1.13 (± 0.99)

Table 2
Characteristics of the infants.

		Virgen del Rocío Hospital (n = 50)	Virgen del Valme Hospital (n = 50)
	Cord pH	7.31 (± 0.05)	7.28 (± 0.07)
	Newborn weight (g)	3506.33 (± 444.85)	3458.55 (± 425.49)
	Newborn height (cm)	49. 31 (± 6.90)	50.55 (± 1.70)
	Head circumference (cm)	34.95 (± 1.44)	35.15 (± 1.49)
Type of delivery	Eutocic	56.00 %	50.00 %
	Vacuum-assisted	10.00 %	15.80 %
	Forceps	4.00 %	13.20 %
	Spatula-assisted	0.00 %	2.60 %
	Cesarean section	30.00 %	18.40 %
Sex	Female	56.30 %	39.50 %
	Male	43.80 %	60.50 %

3.3. Study of correlation between maternal an cord blood mineral elements

The correlation observed between Hg values was the strongest one and significantly different ($r = 0.78$. $p < 0.005$ and being able to stablish the real value of this correlation between 0.69 and 0.85 with a 95 % confidence). The correlations existing for As and Se were also quite high and positive but slightly lower than the one found for Hg, also both showing significant differences ($r = 0.63$. $p < 0.005$, establishing the real value of r between 0.49 and 0.63 with a 95 % confidence and $r = 0.67$, $p < 0.005$ for Se stating with a 95 % confidence a value for r between 0.55 and 0.77), where the levels found in maternal blood are very similar to the ones found in cord blood. The levels found for Zn in both maternal and cord blood were very different with the lowest correlation between them ($r = 0{,}07$, $p = 0{,}57$ and establishing a range for r between −0,13 and 0,96 with a 95 % confidence) in comparison with the rest of metals and metalloids studied. All correlations for the rest of metals and metalloid were positive, except for Cr, Cu and Ni.

3.4. Associations between elements in maternal blood and maternal characteristics

The Mann–Whitney *U* test was run to compare Cd, Cr, Pb and Ni levels in comparison between mothers that stated to be smoking during pregnancy and those who did not but statistically significant differences between the two could not be found (Table 5).

Correlations between rice consumption and As levels were stablished in maternal blood obtaining a positive but quiet low correlation level and not statistically significant ($r = 0.21$, $p = 0.19$). Correlations between Hg, As, Cd and Pb and weekly rice consumption were assessed, being positive for As and Pb ($r = 0.21$, $p = 0.19$ and $r = 0.43$, $p = 0.79$) and negative for Hg and Cd ($r = -0.26$, $p = 0.20$ and $r = -0.52$, $p = 0.03$).

4. Discussion

The aim of the present study was to quantify levels of metals/metalloids in both maternal and cord blood samples of women that had just given birth in two hospitals in the city of Seville, Spain. Women's demographic characteristics, lifestyle and dietary habits were also characterized to try and stablish any kind of correlation between these characteristics and the levels of

Table 3
Descriptive statistics of the metals/metalloid's concentration in maternal blood.

		Hg (μg/L)	As (μg/L)	Cd (μg/L)	Cr (μg/L)	Cu (μg/L)	Mn (μg/L)	Ni (μg/L)	Pb (μg/L)	Se (μg/L)	Zn (μg/L)
Median*		3.03	10.60	0.82	216.24	1632.40	48.76	18.44	10.18	119.78	5088.00
Min		0.05	6.25	0.08	77.80	573.46	14.02	3.18	3.77	55.30	1632.40
Max		28.51	29.68	4.24	421.88	2586.40	2173.00	251.22	80.56	204.58	29,150.00
Percentile	25	1.48	9.54	0.42	182.32	1452.20	25.23	7.42	8.26	105.58	4605.70
	50	3.03	10.60	0.82	216.24	1632.40	48.76	18.44	10.18	119.78	5088.00
	75	4.52	12.72	1.18	242.74	1833.80	1633.46	29.57	13.78	131.44	5830.00
Shapiro-Wilk p*		<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
Mother child correlation (rho)		0.78	0.63	0.30	−0.02	−0.22	0.46	−0.16	0.40	0.67	0.07
Sig. (bilateral)		<0.0005	<0.0005	0.02	0.86	0.08	<0.0005	0.19	0.001	<0.0005	0.57

metals/metalloids found. There are only quite a few studies about pregnant women and mother/children pairs' exposure to metals/metalloids, more commonly heavy metals, and their consequences on the child's development depending on the time and amount of exposure but as far as we know none of the studies developed in Spain has evaluated prenatal exposure to metals and metalloids in maternal and cord blood samples from women living in Sevilla, being this the first one.

Levels of As in blood can be related to environmental or dietary habits such as rice consumption. In the present study, levels of As in maternal blood were tenfold higher than those found by Bocca et al. (2020) in a population of pregnant women recruited in Reus, a city located in the north of Spain, in the area of Catalonia, being our median levels of 10.60 μg/L versus their 1.2 μg/L of As, also similar for cord blood (our median levels of 10.16 μg/L vs their 1.2 μg/L). However, for a study developed in Serbia, under similar inclusion criteria as this one, maternal blood levels (34.8 ± 7.38 μg/L) were a little bit higher than the ones we found (10.60 μg/L), but for umbilical cord, they found 17.2 ± 8.28 μg/L, which are quite similar to the ones found in our population (10.16 μg/L) (Stojsavljević et al., 2021). As for populations outside Europe, a study developed in Río de Janeiro, Brazil, under the PIPA project (Childhood and Environmental Pollutant Project), values of As found for both maternal and cord blood were almost identical to ours (10.27 μg/L and 10.31 μg/L). Strong and statistically significant correlations were found between both placental and maternal blood As levels in all different populations studied, from the ones recruited in Reus to the women from Brazil. These authors concluded that their results explain the ability for this metalloid to easily crossed the placental barrier and get to the umbilical cord (Bocca et al., 2019; de Figueiredo et al., 2020). Cd levels detected in maternal blood from our participants (0.82 μg/L for maternal and 0.73 μg/L for coord blood) were higher than the ones found in Madrid (0.27 μg/L for cord blood and 0.53 μg/L for maternal peripheral blood), a study developed inside of The BioMadrid Project, a biomonitoring project including trios of father-pregnant woman-newborns that live in urban and metropolitan area of Madrid (García-Esquinas et al., 2013). And also, our levels were higher in comparison those found in the population of Reus, Catalonia (0.4 μg/L for maternal and 0.5 μg/L for cord blood versus our 0.82 μg/L and 0.73 μg/L) (Bocca et al., 2019). On the other hand, similar levels of Cd were detected in a cohort of mothers in the Saudi Arabian population (0.98 μg/L for maternal blood and 0.70 μg/L for cord blood) (Al-Saleh et al., 2014). Since for both the Madrid study (García-Esquinas et al., 2013) and also our study, no strong correlation between maternal and cord blood Cd levels could be stablished, this may show the efficiency of the role that the placenta has as a barrier against the passage of this metal. Cr values detected in our participants (216.24 μg/L for maternal blood and 208.82 μg/L for cord blood) were significantly higher than the ones found in cord and maternal blood levels in the Reus cohort (Spain) (0.5 μg/L for maternal blood and 0.6 μg/L for cord blood) (Bocca et al., 2020) and in spite of being the values very similar between both maternal and cord blood, only a very weak and not significant correlation could be established.

Cu levels found in maternal blood (1632.40 μg/L) were more than two fold higher than the ones found in cord blood (655.08 μg/L), with a negative and not too strong correlation, being the values found in cord blood significantly lower, which could indicate a limited transplacental passage of these element from the mother to the fetus, also reported in Barcelona, Germany and even in South Africa (Bocca et al., 2019). Values of Mn (48.76 μg/L for maternal blood and 45.10 μg/L for cord blood) were higher than those found in a Puerto Rico cohort (11.3 μg/L for maternal blood) (Ashrap et al., 2020) and the ones found in the GESTE cohort, a Canadian birth cohort from Quebec (9.35 μg/L for maternal blood) (Serme-Gbedo et al., 2016). A significant and quite strong and positive correlation between Mn in maternal and cord blood was established, indicating that these Mn cord blood levels could come from the maternal blood trough the placenta. Cord blood levels of Ni found in our study (20.14 μg/L) were slightly higher than maternal blood levels (18.44 μg/L). A study that took place in a cohort of pregnant women in a hospital of Beijing, China, found levels for cord blood (6.1 μg/L) that were half the ones found in maternal blood (14.5 μg/L) (Li et al. (2019)) even though they were overall quite similar to the ones found in the present study. However, a negative and weak correlation was established for our values but for the Chinese study, a stronger and positive correlation was stablished. Cord and maternal blood levels of Pb found by García-Esquinas et al. (2013) in father-mother-newborn trios from the urban and metropolitan area of Madrid, were slightly higher than the ones in our study (14.09 μg/L in cord blood versus our 9.51 μg/L and 19.80 μg/L for maternal blood versus the 10.18 μg/L found in this study). These authors had already stated in 2013

Table 4
Descriptive statistics of the metals/metalloid's concentration in cord blood.

		Hg (μg/L)	As (μg/L)	Cd (μg/L)	Cr (μg/L)	Cu (μg/L)	Mn (μg/L)	Ni (μg/L)	Pb (μg/L)	Se (μg/L)	Zn (μg/L)
Median*		4.24	10.16	0.73	208.82	655.08	45.10	20.14	9.51	117.66	2220.70
Min		0.35	4.24	0.08	80.56	293.62	13.67	6.36	3.68	38.16	921.14
Max		52.15	29.68	5.30	340.26	1515.80	95.40	155.82	174.90	185.58	7208.00
Percentile	25	2.21	8.48	0.21	180.20	603.41	38.56	14.38	7.89	108.22	1985.38
	50	4.24	10.16	0.73	208.82	655.08	45.10	20.14	9.51	117.66	2220.70
	75	8.26	12.97	2.12	238.24	708.61	57.24	29.76	12.74	135.96	2597.00
Shapiro-Wilk p*		<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
Mother child correlation (rho)		0.78	0.63	0.30	−0.02	−0.22	0.46	−0.16	0.40	0.67	0.07
Sig. (bilateral)		<0.0005	<0.0005	0.02	0.86	0.08	<0.0005	0.191	0.001	<0.0005	0.57

Table 5
Median with interquartile range (IQR) of maternal blood metals by smoking habits.

Metals	No; Median (IQR)	Yes; Median (IQR)	*p*-Value
Cd	0.94 (0.21–1.06)	0.74 (0.42–2.12)	0.22
Cr	213.06 (189.74–240.62)	204.58 (187.62–233. 20)	0.62
Pb	16.32 (14.59–18.13)	22.472 (8.48–31.80)	0.34
Ni	9.87 (7.72–12.08)	10.60 (8.03–25.24)	0.57

a decrease in blood lead levels that seems to be continuing since our values are even lower than the ones they stated. Li et al. (2019) also found levels a little higher than the ones for the present study, detecting higher concentration in maternal (23.1 μg/L) than in cord blood (14.2 μg/L). Our average concentration of Pb is under the 100 μg/L stated by the Centers for Disease Control and Prevention (CDC)'s to be acceptable for maternal and cord blood levels, being levels above this value considered concerning for adverse health outcomes for newborns (CDC, 2010). Bocca et al. (2020) in pregnant women from Reus, found median concentrations of Ni slightly lower than levels detected in the present study (107 μg/L versus our 119.78 μg/L for maternal blood and 100 μg/L versus our 117.66 μg/L for cord blood). Quite similar values were found in population of pregnant women for Serbia (125 μg/L for maternal and 76.0 μg/L for cord blood) (Stojsavljević et al., 2022). Zn levels detected in cord blood were also lower than the ones found in maternal blood, as was previously observed by Bocca et al. (2019) in Barcelona. In the present study Zn was the element with the highest value detected in maternal and cord blood (5088.00 μg/L and 2220.70 μg/L), also stated for the Reus (Catalonia, Spain) pregnant women that had values similar to the ones on this study (6708 μg/L for maternal and 2311 μg/L for cord blood) (Bocca et al., 2020). Also, Lozano et al. (2022) found in a population of subjects from Valencia, Gipuzkoa and Sabadell cohorts, all of them from the INMA Project, that Zn was the metal present in the highest concentration throughout pregnancy when it was measured in urine (305.18 μg/L). Hg levels in cord blood (4.24 μg/L) were lower than levels detected in the father-mother-child trios from the metropolitan and urban area of Madrid (6.72 μg/L) (García-Esquinas et al., 2013), however, maternal blood levels of Hg were very similar (3.90 μg/L versus the 3.03 μg/L measured on this study). Hg levels detected in both, maternal and cord blood, were lower than the 5.8 μg/L established by the Environmental Protection Agency as the limit for association with health effects (EPA: US). These Hg levels can be attributed to the importance of blue fish consumption in Mediterranean countries.

To sum up, our study concluded that the average values of metals and metalloids measured are quite similar in maternal and cord blood samples, except for Cu and Zn, which are higher in maternal matrix than in cord blood. Our values could indicate that these measured metals are crossing the placental barrier to get to the cord blood and the fetus.

These values could be related to sociodemographic characteristics and lifestyle habits, for instance, the correlation of rice and fish consumption or smoking habits and levels of As and Pb. All of our values fall inside the ranges of non-toxic values for the mother and the development of the fetus, and are also similar to those found by other authors, not only in Europe but also in America and Asia.

As for the strengths of this study, the first one is the measurement of these toxic and essential elements on two different matrices (maternal and cord blood) for a representative cohort of two vulnerable groups, pregnant women and neonates. As a second strength, our study covered an extensive background for this cohort, including many sociodemographic and lifestyle factors with huge impact on these measured levels.

Our preliminary results indicate the need of a more extensive study to further investigate adverse health effects of these pollutants on the development of the fetus and the newborn, and the correlation to other parameters such as oxidative stress or different vitamin values.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Al-Saleh, I., Shinwari, N., Mashhour, A., Rabah, A., 2014. Birth outcome measures and maternal exposure to heavy metals (lead, cadmium and mercury) in saudi arabian population. Int. J. Hyg. Environ. Health 217, 205–218. https://doi.org/10.1016/j.ijheh.2013.04.009.

Ashrap, P., Watkins, D.J., Mukherjee, B., Boss, J., Richards, M.J., Rosario, Z., Vélez-Vega, C.M., Alshawabkeh, A., Cordero, J.F., Meeker, J.D., 2020. Maternal blood metal and metalloid concentrations in association with birth outcomes in northern Puerto Rico. Environ. Int. 138, 105606. https://doi.org/10.1016/j.envint.2020.105606.

Bjørklund, G., Chartrand, M.S., Aaseth, J., 2017. Manganese exposure and neurotoxic effects in children. Environ. Res. 155, 380–384. https://doi.org/10.1016/j.envres.2017.03.003.

Bocca, B., Ruggieri, F., Pino, A., Rovira, J., Calamandrei, G., Martínez, M.Á., Domingo, J.L., Alimonti, A., Schuhmacher, M., 2019. Human biomonitoring to evaluate exposure to toxic and essential trace elements during pregnancy. Part A. Concentrations in maternal blood, urine and cord blood. Environ. Res. 177, 108599. https://doi.org/10.1016/j.envres.2019.108599.

Bocca, B., Ruggieri, F., Pino, A., Rovira, J., Calamandrei, G., Mirabella, F., Martínez, M.Á., Domingo, J.L., Alimonti, A., Schuhmacher, M., 2020. Human biomonitoring to evaluate exposure to toxic and essential trace elements during pregnancy. Part B: predictors of exposure. Environ. Res. 182, 109108. https://doi.org/10.1016/j.envres.2019.109108.

CDC, 2010. Guidelines for the identification and management of lead exposure in pregnant and lactating women. Childhood Lead Poisoning Prevention 2012. 302.

Cerrillos, L., Fernández, R., Machado, M.J., Morillas, I., Dahiri, B., Paz, S., Gonzalez-Weller, D., Gutiérrez, A., Rubio, C., Hardisson, A., Moreno, I., Fernández-Palacín, A., 2019. Placental levels of metals and associated factors in urban and sub-urban areas of Seville (Spain). J. Trace Elem. Med. Biol. 54, 21–26. https://doi.org/10.1016/j.jtemb.2019.03.006.

de Figueiredo, N.D., Araújo, M.S., Luiz, R.R., de Magalhaes Câmara, V., do Couto Jacob, S., dos Santos, L.M.G., Vicentini, S.A., Asmus, C.I.R.F., 2020. Metal mixtures in pregnant women and umbilical cord blood at urban populations—Rio de Janeiro, Brazil. Environ. Scie. Pollut. Res. 27, 40210–40218. https://doi.org/10.1007/s11356-020-10021-w.

García-Esquinas, E., Pérez-Gómez, B., Fernández-Navarro, P., Fernández, M.A., De Paz, C., Pérez-Meixeira, A.M., Gil, E., Iriso, A., Sanz, J.C., Astray, J., Cisneros, M., De Santos, A., Asensio, Á., García-Sagredo, J.M., García, J.F., Vioque, J., López-Abente, G., Pollán, M., González, M.J., Martínez, M., Aragonés, N., 2013. Lead, mercury and cadmium in umbilical cord blood and its association with parental epidemiological variables and birth factors. BMC Public Health 13. https://doi.org/10.1186/1471-2458-13-841.

Gautam, S., Alam, F., Moin, S., Noor, N., Arif, S.H., 2021. Role of ferritin and oxidative stress index in gestational diabetes mellitus. J. Diabetes Metab. Disord. 20, 1615–1619. https://doi.org/10.1007/s40200-021-00911-2.

Karakis, I., Landau, D., Gat, R., Shemesh, N., Tirosh, O., Yitshak-Sade, M., Sarov, B., Novack, L., 2021. Maternal metal concentration during gestation and pediatric morbidity in children: an exploratory analysis. Environ. Health Prev. Med. 26, 1–11. https://doi.org/10.1186/s12199-021-00963-z.

Lee, K.S., Kim, K.N., Ahn, Y.D., Choi, Y.J., Cho, J., Jang, Y., Lim, Y.H., Kim, J.I., Shin, C.H., Lee, Y.A., Kim, B.N., Hong, Y.C., 2021. Prenatal and postnatal exposures to four metals mixture and IQ in 6-year-old children: a prospective cohort study in South Korea. Environ. Int. 157, 106798. https://doi.org/10.1016/j.envint.2021.106798.

Li, A., Zhuang, T., Shi, J., Liang, Y., Song, M., 2019. Heavy metals in maternal and cord blood in Beijing and their efficiency of placental transfer. J. Environ. Sci. (China) 80, 99–106. https://doi.org/10.1016/j.jes.2018.11.004.

Lozano, M., Murcia, M., Soler-Blasco, R., Casas, M., Zubero, B., Riutort-Mayol, G., Gil, F., Olmedo, P., Grimalt, J.O., Amorós, R., Lertxundi, A., Vrijheid, M., Ballester, F., Llop, S., 2022. Exposure to metals and metalloids among pregnant women from Spain: levels and associated factors. Chemosphere 286. https://doi.org/10.1016/j.chemosphere.2021.131809.

Rachman, T., 2018. U.S. EPA, toxicity and exposure assessment for children's health. Angew. Chem. Int. Ed. 6 (11), 951–952 10–27.

Serme-Gbedo, Y.K., Abdelouahab, N., Pasquier, J.C., Cohen, A.A., Takser, L., 2016. Maternal levels of endocrine disruptors, polybrominated diphenyl ethers, in early pregnancy are not associated with lower birth weight in the Canadian birth cohort GESTE. Environ. Health 15, 1–11. https://doi.org/10.1186/s12940-016-0134-z.

Stojsavljević, A., Rovčanin, M., Rovčanin, B., Miković, Ž., Jeremić, A., Perović, M., Manojlović, D., 2021. Human biomonitoring of essential, nonessential, rare earth, and noble elements in placental tissues. Chemosphere 285. https://doi.org/10.1016/j.chemosphere.2021.131518.

Stojsavljević, A., Rovčanin, M., Miković, Ž., Perović, M., Jeremić, A., Zečević, N., Manojlović, D., 2022. Analysis of essential, toxic, rare earth, and noble elements in maternal and umbilical cord blood. Environ. Sci. Pollut. Res. https://doi.org/10.1007/s11356-021-18190-y.

Tatsuta, N., Nakai, K., Kasanuma, Y., Iwai-Shimada, M., Sakamoto, M., Murata, K., Satoh, H., 2020. Prenatal and postnatal lead exposures and intellectual development among 12-year-old japanese children. Environ. Res. 189, 109844. https://doi.org/10.1016/j.envres.2020.109844.

Weyde, K.V.F., Olsen, A.K., Duale, N., Kamstra, J.H., Skogheim, T.S., Caspersen, I.H., Engel, S.M., Biele, G., Xia, Y., Meltzer, H.M., Aase, H., Villanger, G.D., 2021. Gestational blood levels of toxic metal and essential element mixtures and associations with global DNA methylation in pregnant women and their infants. Sci. Total Environ. 787, 147621. https://doi.org/10.1016/j.scitotenv.2021.147621.

Wu, W., Lu, J., Ruan, X., Ma, C., Lu, W., Luo, Y., Luo, D., Mu, X., 2021. Maternal essential metals, thyroid hormones, and fetal growth: association and mediation analyses in chinese pregnant women. J. Trace Elem. Med. Biol. 68, 126809. https://doi.org/10.1016/j.jtemb.2021.126809.